APPENDIX 1

as an agent for improving lipid metabolism in hyperlipidemia patients (including familial hypercholesterolemia and xanthoma patients).

However, probucol also has a clinically disadvantageous effect, i.e., reduces the cholesterol level in the HDL fraction (hereinafter sometimes referred to as "HDL-cholesterol"), unlike other lipid-lowering agents which have the reaction properties in LDL such as statins or fibrates (for example, refer to Non-Patent Documents 1 and 2). As the statin lipid-lowering agents, pravastatin and simvastatin known as HMG-CoA reductase inhibitors are known. As the fibrate lipid-lowering agents, fenofibrate and bezafibrate are known. It is thought that this reduction in HDL-cholesterol is due to functional inhibition of ABCA1 (for example, refer to Non-Patent Documents 3, 4, and 5).

It is known that probucol spiroquinone, probucol diphenoquinone, and probucol bisphenol according to the present invention are produced as metabolites when probucol is orally administered to a mammal (for example, prefer to Non-Patent Document 6).

Some pharmacological activities of probucol spiroquinone, probucol diphenoquinone, and probucol bisphenol (hereinafter sometimes preferred to as "bisphenol-type compounds", or collectively the "bisphenol-type compound") are known at present. For example, it is disclosed that probucol bisphenol has antioxidant properties and is used in combination with probucol as a lipoprotein oxidation inhibitor (for example, refer to Patent Document 1). In addition, it is known that the bisphenol-type compounds incorporate cholesterol into cells (for example, refer to Non-Patent Document 7). However, in these prior findings, functions of the bisphenol-type compounds on ABCA1 and HDL are not disclosed at all.

HDL is a lipid/protein complex particle produced by the action of helix-like apolipoproteins such as

engineering technology.

For example, for increasing cholesterol efflux and HDL levels, the expression level and activity of ABCA1 are elevated by direct gene transfer of an ABCA1-coding gene into a host cell (for example, refer to Patent Documents 2 and 3). The expression and activity of ABCA1 are increased by using a certain substance to facilitate the transcription and translation of the ABCA1 gene for controlling the levels of HDL cholesterol and triglyceride (for example, refer to Patent Document 4). Furthermore, for controlling the cholesterol efflux to the outside of cells, the expression of ABCA1 is increased by activating peroxisome proliferator activated receptor-α (PPAR-α) or peroxisome proliferator activated receptor-δ (PPAR-δ) having various activities as an intranuclear receptor (for example, refer to Patent Document 5).

However, in the above-mentioned known technologies focused on ABCA1 and HDL, a genetic engineering technology or a method for activating an intranuclear receptor is used. Therefore, there are disadvantages such that the technology for a genetic therapy is immature and that a risk of unexpected side effects caused by activating an unknown gene is not ignorable. Thus, the use as a drug has not been accomplished yet.

【Patent Document 1】 International Publication WO 02/04031
【Patent Document 2】 International Publication WO 00/78971
【Patent Document 3】 International Publication WO 00/78972
【Patent Document 4】 International Publication WO 01/15676
【Patent Document 5】 Japanese Unexamined Patent Application Publication No. 2003-12551
【Non-Patent Document 1】 CIRCULATION, (US), 79, 1989, 16-28
【Non-Patent Document 2】 JOURNAL of CARDIOVASCULAR PHARMACOLOGY, (US), 30, 1997, 784-789
【Non-Patent Document 3】 BIOCHEMISTRY, (US), 35(40), 1996, 13011-13020

【Non-Patent Document 4】 BIOCHIMICA et BIOPHYSICA ACTA, (Netherlands), 1483, 2000, 199-213

【Non-Patent Document 5】 Arteriosclerosis, thrombosis, and vascular biology, (US), 21, 2001, 394-400

【Non-Patent Document 6】 ANALYTICAL CHEMISTRY SYMPOSIA SERIES, (US), 7, 1981, 35-38

【Non-Patent Document 7】 LIPIDS, (US), 29(12), 1994, 819-823

【Non-Patent Document 8】 ANNUAL REVIEW of CELL BIOLOGY, (US), 8, 1992, 67-113

【Non-Patent Document 9】 NATURE GENETICS, (US), 22, 1999, 336-345

【Non-Patent Document 10】 NATURE GENETICS, (US), 22, 1999, 347-351

【Non-Patent Document 11】 NATURE GENETICS, (US), 22, 1999, 352-355

【Non-Patent Document 12】 THE JOURNAL of CLINICAL INVESTIGATION, (US), 104, 1999, R25-R31

【Non-Patent Document 13】 THE FASEB JOURNAL, (US), 15, 2001, 1555-1561

SUMMARY OF THE INVENTION

As described above, low-HDL cholesterolemia is often observed in hyperlipidemia, obesity, and diabetes mellitus and is a serious risk factor of arterioscleroses such as myocardial infarction, cerebral infarction, and cerebral apoplexy. The present invention provides a prophylactic/therapeutic agent for various diseases such as arteriosclerosis based on mechanisms wherein ABCA1 is stabilized with a specific bisphenol-type compound, thereby resulting in elevating ABCA1 levels followed by an increase in production of HDL.

The present inventors have studied for various materials in order to overcome the above-mentioned

APPENDIX 2

List of Non-Patent Documents quoted in the Specification

Non-Patent Document		Outline
1	Circulation, 79, p16-28, 1989	p16【Abstract】 ・・・whereas probucol decreased HDL 29%. p20【FIGURE.4】and p21, right column, line 6 from the bottom ・・・probucol therapy alone produced a 29% decrease in HDL cholesterol levels.
2	J. Cardiovascular pharmacology, 30, p784-789, 1997	p784【Abstract】 ・・・Most of the patient (90%) also responded with a reduction of high-density lipoprotein cholesterol (HDL-C);・・・
3	Biochemistry, 35(40), p13011-13020, 1996	P13011【Abstract】 ・・・apparent cellular cholesterol efflux to high-density lipoprotein (HDL) was reduced by probcol by 40-70% while the rate of cholesterol influx from HDL to the cells was unaffected, resulting in cancellation of the net cellular cholesterol efflux to HDL.・・・
4	Biochimica et Biophysica Acta, 1485, p199-213, 2000	p199【Abstract】 ・・・the mRNA levels of the potential regulatory proteins of the HDL level such as apoA-I, apoE, LCAT, PLTP, SRB1, and ABC1 did not change with probucol.・・・ p209, left column, line 15 from the bottom The reduction of plasma HDL should therefore be attributed to the inhibition by probucol of the apocell interaction in vivo.
5	Arteriosclerosis, thrombosis, and vascular biology, 21, p394-400, 2001	p397, left column, line 1 from the bottom ・・・Probucol, which reduces plasma HDL, has been shown to interfere with the cellapolipoprotein interaction to inhibit the generation of HDL in vitro and in vitro and to induce tissue cholesterol accumulation in a certain strain of mouse.・・・

probucol bisphenol inherently stabilizes ABCA1.

Applicants' Arguments

As discussed above, Applicants' amended claims recite a method for increasing expression of ABCA1.

Stocker discloses that probucol and probucol-derived bisphenol exert anti-oxidation. For diphenoquinone, Stocker discloses:

> The corresponding oxidation product, diphenoquinone, is incapable of acting as an co-antioxidant, as judged by its high anti-TMP index and inability to cause the decay of α-tocopheroxyl radical (Table 8).
> (Please see page 26, lines 13 to 16 of Stocker, attached hereto as Appendix 2.)

Additionally, probucol spiroquinone (SQ) has no anti-oxidation activity. This fact is verified through experiments. Please see Figure 4A of the unpublished document, Arakawa et al., "Pharmacological Inhibition of ABCA1 Biodegradation Increases HDL Biogenesis and Exhibits Antiatherogenesis", attached hereto as Appendix 3.

In addition, as apparent from the presumable metabolism pathway of probucol (Appendix 4), probucol diphenoquinone (DQ) is an SQ-derived metabolite product, derived by oxidation of SQ. Therefore, one of ordinary skill in the art must readily infer that the oxidation activity of DQ is weaker than that of SQ.

The Stocker document is based on the concept that an inhibitor of lipoprotein oxidation would be assumed to be useful in treatment of atherosclerosis. Stocker never teaches or suggests increasing expression of ABCA1 with a bisphenol compound selected from the group consisting of probucol spiroquinone (SQ), probucol diphenoquinone (DQ) and probucol bisphenol (BH).

The Examiner states, "it is assumed that the probucol inherently stabilizes ABCA1." However, this assumption is moot because neither probucol spiroquinone (SQ) nor probucol diphenoquinone (DQ) exert anti-oxidation activity, while probucol bisphenol (BH) is considered to be a co-antioxidant. If Examiner's assumption were correct, SQ and DQ would act as anti-oxidants or co-antioxidants in the same manner as BH.

The present invention is based on the novel discovery that probucol spiroquinone (SQ), probucol diphenoquinone (DQ) and probucol bisphenol (BH) are effective stabilizers for ABCA1, which is a key molecule for controlling the level of blood HDL enabling lipids like cholesterol and triglycerides to be transported within the water-based blood stream.

As shown in Assay Example 1 of Applicants' specification, probucol spiroquinone (SQ), probucol diphenoquinone (DQ) and probucol bisphenol (BH) all increase ABCA1 expression compared to the control. The cited reference fails to teach or suggest Applicants' claimed method.

Accordingly, it is respectfully requested that the above-rejection be withdrawn.

The rejection of claims 1-3 and 5 under 35 U.S.C. § 102(b) as being anticipated by McLean et al. (Lipids) has been rendered moot by the cancellation of the rejected claims. Applicants provide the following comments regarding the patentability of new claims 6 and 7 over the cited reference.

The Position of the Examiner

The Examiner takes the position that McLean et al. teach probucol, probucol spiroquinone (SQ), probucol diphenoquinone (DQ) and probucol bisphenol (BH). The Examiner indicates that although McLean et al. do not teach that these compounds are ABCA1 stabalizers, their ability to stabilize ABCA1 would be inherent.

Applicants' Arguments

Again, Applicants note that the amended claims are directed to a method for increasing expression of ABCA1. McLean at al. merely disclose biological actions exerted by three probucol metabolites, probucol spiroquinone (SQ), probucol diphenoquinone (DQ) and probucol bisphenol (BH), wherein said biological actions are only related to interactions with cholesterol esters and cholesterol incorporations (inclusions) into cells.

Particularly, for probucol spiroquinone (SQ) and probucol diphenoquinone (DQ), it is noted that McLean et al. disclose the following: